RESEARCH ON ETHICAL ISSUES IN HUMAN STUDIES

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National Cancer Institute (NCI)
(http://www.nci.nih.gov/)
National Heart, Lung, and Blood Institute (NHLBI)
(http://www.nhlbi.nih.gov/index.htm)
National Human Genome Research Institute (NHGRI)
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National Institute on Aging (NIA)
(http://www.nia.nih.gov/)
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
(http://www.niaaa.nih.gov/)
National Institute of Allergy and Infectious Diseases (NIAID)
(http://www.niaid.nih.gov/default.htm)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.niams.nih.gov/)
National Institute of Child Health and Human Development (NICHD)
(http://www.nichd.nih.gov/)
National Institute on Deafness and Other Communication Disorders (NIDCD)
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National Institute of Dental and Craniofacial Research (NIDCR)
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National Institute on Drug Abuse (NIDA)
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National Institute of Mental Health (NIMH)
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(http://www.nih.gov/fic/)
Office of Behavioral and Social Sciences Research (OBSSR)
(http://obssr.od.nih.gov/)
Office of Research on Women's Health (ORWH)
(http://www4.od.nih.gov/orwh/)

THIS PA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS PA

This PA replaces PA-99-079.

The National Institutes of Health (NIH) invite research grant applications (R01) to investigate ethical issues in human subjects research. The Code of Federal Regulations - Protection of Human Subjects (45 CFR, Part 46) provides a regulatory framework that all NIH-supported researchers must follow. Recent developments in biomedical and behavioral research, however,

including the rapid growth of new interventions and technologies (e.g., stem cells, genetics research), increasing involvement of foreign populations in clinical research, and concerns about financial conflicts of interest among researchers, challenge investigators' abilities to interpret and apply the regulations. Other situations (e.g., research with vulnerable populations, the use of data banks or archives, research on stigmatizing diseases or conditions) may present difficulties for identifying strategies, procedures, and/or techniques that will enhance/ensure the ethical involvement of human participants in research. The purpose of this program announcement is to solicit research addressing the ethical challenges of involving human participants in research in order to inform and optimize protections for human participation in research.

RESEARCH OBJECTIVES

In pursuing NIH-funded human research, investigators, institutions, and IRB members must adhere to several general ethical principles, including: Respect for Persons - individuals should be treated as autonomous agents and persons with diminished autonomy are entitled to additional protections; Beneficence - efforts must be made to maximize possible benefits and minimize possible harms; and Justice - individuals or groups of individuals should not be unduly burdened as a result of participating in research and individuals or groups of individuals should not disproportionately benefit as a result of participating in research (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm).

Interpreting and applying these ethical principles, however, can present questions or dilemmas for investigators. For example, in some circumstances, it may be difficult for investigators and members of Institutional Review Boards (IRBs) to: identify and minimize all forms of risks or harms; know how best to inform potential human participants in order that they comprehend research risks and voluntarily consent to participate; or, identify and then implement procedures that will safeguard the rights and welfare of participants considered vulnerable to undue influence. Ensuring consistency with stated principles may be particularly challenging when working with non-Western cultures or in foreign countries where the very concepts and meaning of "individual," "risks," "benefits," "informed consent," etc. may be very different and/or where the standards for conducting research may be at odds with US standards. In addition, constant advances in communication and information technologies affect how research data are defined, recorded, stored, and maintained, thereby providing new challenges for maintaining privacy and confidentiality.

In conducting research on ethical issues in human subjects research, several different conceptual frameworks for ethics (e.g., principlism, deontology, utilitarianism, ethics of rights, ethics of care,

etc.) exist and may provide presuppositions and theoretical foundations from which bioethical questions can be formulated and tested. It is important to remember that the questions and strategies for testing these issues must be consistent with existing federal requirements. Currently, research supported by the Department of Health and Human Services (DHHS – which includes NIH) follows the Code of Federal Regulations (45 CFR, Part 46) – Protection of Human Subjects (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm). For research conducted internationally, alternative guidelines that are consistent with 45 CFR 46 may be used (http://ohrp.osophs.dhhs.gov/humansubjects/assurance/filasur.htm), such as those developed by the World Health Organization, the Council for International Organizations of Medical Sciences, and other internationally recognized groups.

In addition, the research design for conducting research on ethical issues in human studies should be appropriate to the nature of the project(s) proposed and the disciplines involved. Given the conceptual and methodological complexity of many of these research questions, interdisciplinary and collaborative projects are encouraged, particularly those involving clinical researchers, ethicists, and behavioral/social scientists.

The purpose of this PA is to support empirical research addressing the ethical challenges of involving human participants in research in order to inform and optimize protections for human participation in research. Examples of the types of topics that would be appropriate for applications submitted under this announcement include, but are not limited to, the following:

MINIMIZING RISKS in HUMAN RESEARCH

o Assess how features of the research and research setting affect evaluations of risks versus potential benefits of different types of research (e.g., use of placebo, Phase I, II, III clinical trials) for investigators, IRB members, and potential participants/ groups/ communities. Examples of features of the research or research setting may include:
- Characteristics of the participant (e.g., age, health status and stage of disease, ethnic/cultural background, cognitive capacity, social status, gender, incarceration);
- Aspects of the condition/disease (e.g., prevalence, severity, chronicity, degree of disability);
- Nation or culture in which the study will take place.

o Identify potential social, psychological, and/or economic harms (e.g., stigma, discrimination, personal distress, loss of insurance coverage, loss of employment) that may be associated with recruitment, participation, self-determined or study-determined withdrawal from research. Evaluate strategies or procedures for minimizing these harms in regard to

individuals/groups/communities/populations' willingness to participate in different types of research.

o Assess the conditions and assumptions under which IRB evaluation of risk vs. potential benefits is similar or different from the evaluation of risks vs. potential benefits by individuals/groups/communities/populations.

o Assess the impact of obtaining a Certificate of Confidentiality on perceptions of IRB members and/or participants in terms of evaluation of risks, understanding of the research, and/or understanding of the rights to privacy.

o Identify and evaluate strategies for protecting and minimizing disclosure of private information when identifiable data are:
- Collected via the internet
- Preserved for secondary analysis, e.g., a tissue or gene bank, data archive or warehouse;
- Collected about third parties in research, e.g., network studies.

ISSUES in INFORMED CONSENT

o Determine how features of the informed consent process affect participants' comprehension and/or willingness to participate in research. Examples of these features include:
- Variations in the style of presentation (e.g. oral, written, graphic, video);
- Readability, complexity, and or format of the consent document;
- Characteristics of the participant (e.g. language preference, age, health status, education, cultural/ethnic background, personal motivations, cognitive capacity);
- Contextual features or circumstances in which informed consent takes place (e.g., characteristics of the research staff, location such as research hospital vs. private office vs. home, presence/involvement of family members, presence/involvement of patient advocates).

o Evaluate different methods and identify best-practice strategies for consulting with communities in the United States and/or other countries regarding comprehension, willingness to participate, and/or willingness to continue with research at the individual, group/community, and/or population level.

o Assess how re-contacting participants to obtain informed consent for additional uses of their data affects participant comprehension, willingness to participate, and sense of coercion.

o Identify and evaluate strategies, procedures, and/or techniques for improving comprehension of research by individuals, groups/communities, and /or populations at the time of initial consent, during, and/or after completion of the study. Also, determining how these strategies may differ depending on age, health status, ethnic/cultural background, cognitive capacity, social status, and/or gender of the target audience.

o Assess how participants' willingness to participate versus sense of coercion, may be affected by:
- Use of different types of incentives, remuneration, and/or provision of medical care;
- Different features of the research setting, e.g., personal physician as recruiter and/or researcher, private funding versus federal funding;
- Characteristics of the participant, e.g., health status, age, ethnic/cultural background, education, gender.

o Assess the impact of communicating or not communicating individual test results, study progress, and/or study results on participants' willingness to continue with the protocol and/or participate in research again.

OVERSIGHT OF RESEARCH and RESEARCH DATA

o Identify and evaluate strategies to improve the oversight of human participants protection by Institutional Review Boards (IRB), Data and Safety Monitoring Boards (DSMB), Conflict of Interest (COI) committees, etc. Examples may include:
- Develop and evaluate best practice outcome measures for decision-making about the acceptability of research protocols;
- Assess the consistency of protocol review decisions within DSMBs, IRBs, or COI Committees;
- Assess the impact of conflicts of interest among members of oversight committees on decision-making about the acceptability of research protocols, interpretations of adverse events, and/or perceptions of "independence of review" by the research community.
- Assess the impact of disclosing varying degrees of financial conflicts of interest involving the principal investigator, members of oversight committees, sponsor, institution, etc. on research participant willingness to participate and/or continue with research, and/or participant understanding of the research.

o Compare and evaluate different methods and strategies for identifying, reporting, and handling adverse events based on the perspectives of individual participants, institutions, DSMBs, and/or IRBs.

MECHANISM OF SUPPORT

This PA will use the NIH R01 award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign
o Faith-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

Also, new investigators are encouraged to apply. They may wish to develop small, focused research projects that provide initial findings for larger research proposals in the future. It would be expected that such applications also would have smaller budgets reflecting the scope of the research proposed.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Since this PA involves a number of NIH Institutes, we are providing: (a) a General NIH Contact, to assist with general questions about the PA and help direct applicants to relevant Institute/Office Contacts; and (b) Specific NIH Institute/Office Contacts to answer questions about Institute/Office specific scientific/research issues and financial or grants management issues. We strongly encourage you to identify and correspond with Institute/Office Contacts prior to submitting your application.

o Direct your general questions about this program announcement to:

Della M. Hann, Ph.D.
Office of Extramural Research
NIH
Building 1, Room 152
Bethesda, MD 20892
Telephone: (301) 402-2725
FAX: (301) 402-3469
Email: hannd@od.nih.gov

To assist in identifying which Institute/Office most closely matches your research topic, the following web site provides additional information about Institute/Office specific research interests that will be supported by this PA http://grants.nih.gov/grants/funding/ethics_contacts.htm.

o Direct your questions about scientific/research issues to (be sure to identify the Institute/Office that most closely matches your topic):

National Cancer Institute
Mary S. McCabe
Bldg. 31 Room 3A-44
Bethesda, MD 20892
Telephone: (301) 496-6404
FAX: (301) 496-0826
Email: mccabem@mail.nih.gov

National Heart, Lung, and Blood Institute
Ellen M. Werner, Ph.D
6701 Rockledge Drive, Room 10156, MSC 7950

Bethesda, MD 20892-7950
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FAX: (301) 480-0868
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National Human Genome Research Institute
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Building 31, Room B2B07
31 Center Drive, MSC 2033
National Institutes of Health
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National Institute on Aging
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DAIT

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o Direct your questions about financial or grants management matters to:

National Cancer Institute
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SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR:
Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than $500,000 must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does

not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review
o Availability of funds
o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html) ; a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.
The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and

ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people. http://grants.nih.gov/grants/guide/pa-files/PA-02-015.html.

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